

REMARKS:

This is a full and complete response to the Office action dated December 24, 2008. Favorable reconsideration of the claims is respectfully requested.

REGARDING THE CLAIMS:

Claims 11-12, 14-18, 23-30 are pending in the application. Claim 14 and 15 have been amended for clarification with support found on page 6 of the application. No new matter has been added.

IN RESPONSE TO THE OFFICE ACTION:

REJECTION UNDER 35 U.S.C. § 112:

Claims 14 and 15 stand rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular the Examiner argues that without the recitation of a sequence identifier (i.e. SEQ ID NO), it is not clear to the Examiner as to which amino acids applications are referring to. Furthermore, Examiner indicated it was not understood how “a mutant P450 monooxygenase is a F87A, F87V, L188K, V26T, R47F and V26T.” While Applicants believe said claim is clear without amendment, in an effort to expedite prosecution, Applicants have amended claims 14 and 15 to include the recitation of a “SEQ ID NO:35” and further clarified the recitations of the mutations in said claims. Accordingly, as Applicants have complied with Examiner’s suggestion, withdrawal of the above mentioned rejection is respectfully requested.

REJECTION UNDER 35 U.S.C. § 103(a):

Claims 11-12, 14, 16-18, 23-30 stand rejected under 35 USC §103(a) as being unpatentable over **Estabrook et al.** (hereinafter “**Estabrook**”) in view of **Creaser et al.** (hereinafter “**Creaser**”), **Voss et al.** (hereinafter “**Voss**”) and **Oliver et al.** (hereinafter “**Oliver**”). Applicants respectfully traverse this rejection.

The Examiner asserts that **Estabrook** discloses a method for the enzymatic production of terminally or subterminally hydroxylated fatty acids comprising hydroxylating fatty acids in the presence of an electron donor system, a cytochrome P450 monooxygenase, oxygen, chloride ions and a hydrogen peroxide cleaving enzyme.

The Examiner further asserts that **Creaser** discloses a Zn/Co(III)sepulchrate electron donor system, and teaches that Zn dust causes reduction of the Co(III)sepulchrate mediator within seconds.

Additionally, the Examiner argues that **Voss** discloses that enzymes undergo denaturation on metal electrodes eventually inactivating the enzyme.

The Examiner also states that **Oliver** discloses a mutant of SEQ ID NO:35 having a F87A mutation which hydroxylates fatty acids at the ω position, unlike the wildtype enzyme.

It is asserted by the Examiner that it would have been obvious to one having ordinary skill in the art to modify the method of **Estabrook** in hydroxylating fatty acids at the ω position by using the mutant cytochrome P450 monooxygenase of **Oliver** and using Zn dust as taught by **Creaser**. It is further asserted by the Examiner that one of ordinary skill in the art would have been motivated to use Zn dust because **Creaser** teaches that Zn dust causes immediate reduction, Zn dust is widely available, and because **Voss** teaches that proteins denature on metal electrodes. Therefore, the Examiner holds that the above mentioned claims are prima facie obvious.

Applicants respectfully disagree. While the reference **Voss** describes the denaturation of a specific metalloprotein (cytochrome c) at an electrode surface, Applicants submit that the conditions under which this observation takes place are completely disregarded in the Office Action. When such conditions are taken into account, such teaches against the Examiner's proposition regarding motivation. In other words, the Examiner uses impermissible hindsight to pick and choose from the reference, ignoring what was actually known at the time of filing of the presently claimed invention. *KSR, 82 USPQ.2d* 1385; 127 S. Ct. 1727, 1745 (2007) ("A factfinder should be aware, of

course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning”); MPEP §2145 (X).

Applicants submit that **Voss** has provided an electrically heated electrode in order to observe conformational changes of enzyme as a function of temperature. Therefore, unfolding or denaturation of the protein as observed according to **Voss** is **not** an undesired effect. Rather it is intended to be further investigated. As taught by **Voss** at the end of the reference’s article:

“...an electrically-heated electrochemical sensor, in combination with differential pulse voltammetry, has been shown to be extremely useful for probing the conformational changes and unfolding process of cytochrome c with increased temperature at bare gold electrodes. The merit of the technique is that it enables high temperatures to be used at the electrode whilst the protein is at ambient temperatures in buk solution. Further work will address more detailed aspects this transition and empmploy pulsed heating techniques to reach higher temperatures. **Applications to other Redox proteins can be anticipated.**” [Emphasis added].

As can be seen from the above, **Voss** teaches the very opposite of that which the Examiner alleges is derived from the reference. The reference does not teach that the use of electrodes has to be avoided. Rather, according to **Voss**, the use of the electrode system as disclosed there **should be extended to further Redox proteins.** Therefore, Applicants respectfully submit that the Examiner’s conclusion that one of skill in the art would be motivated to avoid use the electrode system and instead use Zn dust because **Voss** indicates that denaturation of the enzyme takes place - this has absolutely no basis in the reference, in fact the opposite teaching can be taken from **Voss**. Accordingly, Applicants submit that Examiner’s assertions are based merely impermissible hindsight and therefore no prima facie case of obviousness may be established.

Moreover, Applicants submit that the conventional electroenzymatic processes applying electrodes (which has nothing to do with the scientific test system of Voss) are performed with thermal control (see for example Estabrook, p. 48, section “Reaction System”) describing temperature equilibrium at 37 °C, i.e. non heating conditions.

Nothing can be taken from **Estabrook** suggesting to avoid electrodes in view of a risk of protein denaturation at the electrode. To the contrary, as stated therein:

“no significant destruction of the P450 catalyst”

is explicitly taught. *Estabrook*, p. 50, comments, paragraph 1.

Accordingly, Applicants submit that the motivation suggested by the Examiner finds no support in the cited references or state of the art. As noted by the Supreme Court in KSR, “rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR International Co. v. Teleflex Inc.*, 82 USPQ.2d 1385, quoting *In re Kahn*, 441 F.3d 977, 988 (C.A.Fed.2006). Accordingly Applicants submit that no prima facie case of obviousness may be established.

Additionally, and as discussed in the reply filed May 29th, 2008, Applicants submit that there is absolutely no guidance, teaching or suggestion in **Creaser** to use Zn dust in a biochemical system. There is no experimental guidance nor is there hypothetical guidance in the reference. To the contrary, at the end of the reference, it is speculated to use in organic and inorganic chemistry to use as therapeutic agents – still without any experimental guidance. *Creaser*, p. 3182, right col. 2nd paragraph. Potential biochemical applications are not at all mentioned, taught or suggested.

Furthermore, as also discussed in the reply filed May 29, 2008, p. 11 and the experimental work submitted February 12, 2004, Applicants compared reaction rates for B-3 mutant F87-A under conditions similar to the cited art and also to the claimed invention. Artificial substrate 12-pNCA was used as the enzyme substrate to measure activity via an optical test. Enzyme activity was measured in separate reactions in either the presence of NADPH or electrolysis/Pt-electrode (**Estabrook**) and NADPH or Zn dust and Co(III)sepulchrate as electron sources. With the NADPH reactions set to 100%, the results showed that Zn dust and Co(III) sepulchrate reaction had a relative reaction almost twice as great as that of the **Estabrook** example. These data show that the electron donor system of the instant claims is more suitable for enzyme reactions as

claimed because of the higher reaction rates. Such **superior** results cannot be expected from the disclosures of the cited references and the knowledge in the art at the time of filing. Accordingly, for this reason also, the present claims are not obvious in view of the cited references or assertions made in the Office Action.

In view of the comments above, it is respectfully requested that the rejections be withdrawn and a Notice of Allowance issue with respect to the currently pending claims.

The undersigned representative requests any extension of time that may be deemed necessary to further the prosecution of this application.

The undersigned representative authorizes the Commissioner to charge any additional fees under 37 C.F.R. 1.16 or 1.17 that may be required, or credit any overpayment, to Deposit Account No. 14-1437, referencing Attorney Docket No.: PF 50531.

In order to facilitate the resolution of any issues or questions presented by this paper, the Examiner may directly contact the undersigned by phone to further the discussion.

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Respectfully submitted,

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